L7: Entry 133 of 146 File: USPT Mar 21, 2000

5807540

DOCUMENT-IDENTIFIER: US 6040333 A
TITLE: Dietary supplements

Brief Summary Text (5):
In general, women pass through three principal adult developmental or life stages--the childbearing or pre-perimenopausal stage; the perimenopausal and menopausal stage; and the post-menopausal stage. Numerous health conditions and risks may develop during each of these life stages. They include coronary heart disease (CHD), some cancers, cervical dysplasia, menopause, osteoporosis, pre-menstrual syndrome (PMS), iron deficiency anemia, and fetal neural tube defects. The incidence of these conditions and risks varies with each life stage and has been shown to be influenced by diet and dietary supplements.

Brief Summary Text (6):
CHD is a major cause of death in women. It claims the lives of nearly 250,000 women per year, most of whom are post-menopausal. Although generally not manifest until the post-menopausal stage, CHD develops over decades. Well established risk factors for CHD include elevated plasma cholesterol levels and abnormal glucose metabolism. Also implicated in the development of CHD are elevated homocysteine levels and the effects of free radicals. Phytoestrogens, antioxidants, chromium and folic acid have been shown to mitigate these risk factors.

Brief Summary Text (7):
In general, the risk of cancer increases with age. Breast cancer, which afflicts one in every nine women, is chief among women's concerns. Both antioxidants and phytoestrogens appear to have a role in the prevention of some cancers, particularly breast cancer. Furthermore, folic acid has been shown to reduce the risk of cervical dysplasia, which is a precursor to cervical cancer.

Brief Summary Text (12):
Fetal neural tube defects may occur during the first month of gestation, often before a woman is aware of her pregnancy. Folic acid prevents fetal neural tube defects and, therefore, should be consumed in sufficient quantities by women of child-bearing age.

Brief Summary Text (16):
In one embodiment of this aspect of the invention there is provided a dietary supplement for supplementing the micronutrient and phytochemical needs of pre-perimenopausal women to prevent or reduce the risk of fetal neural tube defects, iron deficiency anemia, PMS, osteoporosis, coronary heart disease, cervical dysplasia and some cancers throughout that stage and the rest of a woman's life, comprising about 200 to about 500 mg calcium, about 100 to about 200 mg magnesium, about 0.5 to about 1.5 mg boron, about 0.5 to about 1.5 mg copper, about 2 to about 2.6 mg manganese, about 10 to about 13 mg zinc, about 200 to about 300 IU vitamin D, about 12 to about 18 mg iron, about 400 to about 440 .mu.g folic acid, about 2 to about 10 .mu.g vitamin B.sub.12, about 50 to about 100 mg vitamin B.sub.6, about 50 to about 100 .mu.g chromium, about 100 to about 200 IU vitamin E, about 100 to about 1000 mg vitamin C and about 8 to less than 50 mg phytoestrogen in admixture with a biologically acceptable carrier.

Brief Summary Text (17):
In another embodiment of this aspect of the invention the dietary supplement is formulated to supplement the changing nutritional needs of perimenopausal and menopausal women for the prevention or reduction of the risk of PMS, symptoms of menopause, fetal neural tube defects, osteoporosis, CHD, cervical dysplasia and some forms of cancer throughout that stage and the rest of a woman's life. This dietary

supplement comprises from about 200 to about 1000 mg calcium; from about 100 to about 200 mg magnesium; from about 1.5 to about 2.5 mg boron; from about 1.5 to about 2.5 mg copper; from about 2.4 to about 3.6 mg manganese; from about 12 to about 15 mg zinc; from about 300 to about 400 IU vitamin D; from about 10 to about 15 mg iron; from about 400 to about 440 .mu.g folic acid; from about 2 to about 15 .mu.g vitamin B.sub.12 ; from about 50 to about 100 mg vitamin B.sub.6 ; from about 75 to about 200 .mu.g chromium; from is about 200 to about 400 IU vitamin E; from about 200 to about 1000 mg vitamin C; and from about 10 to less than 50 mg phytoestrogen in admixture with a biologically acceptable carrier.

Brief Summary Text (18):
In yet another embodiment of this aspect of the invention the dietary supplement is formulated to supplement the increased nutritional needs of post-menopausal women for the prevention or reduction of the risk of coronary heart disease, some forms of cancer and osteoporosis throughout the final stage of her life. This dietary supplement comprises about 200 to about 1500 mg calcium, about 150 to about 250 mg magnesium, about 2.5 to about 3.5 mg boron, about 2.5 to about 3.5 mg copper, about 4.4 to about 5.6 mg manganese, about 15 to about 18 mg zinc, about 300 to about 800 IU vitamin D, about 5 to about 10 mg iron, about 400 to about 440 .mu.g folic acid, about 2 to about 18 .mu.g vitamin B.sub.12, about 1.6 to about 10 mg vitamin B.sub.6, about 100 to about 200 .mu.g chromium, about 350 to about 800 IU vitamin E, about 300 to about 1000 mg vitamin C and about 10 to less than 50 mg phytoestrogen in admixture with a biologically acceptable carrier.

Detailed Description Text (2):
The present invention provides dietary supplements for women that are designed to meet a woman's health needs at each particular stage of her life, such as pre-perimenopause, perimenopause and menopause, or post-menopause, or during transition from one such life cycle into the next. This is accomplished by supplying, in the dietary supplements of the invention, a variety of nutrients that address common health risks associated with each of these life stages. Thus, each of the dietary supplements of the present invention provides a variety of nutrients, including antioxidants to increase the resistance of LDL cholesterol to oxidation, elements to enhance calcium absorption and utilization, nutrients to address iron deficiency anemia, folic acid to prevent fetal neural tube defects, compounds to reduce serum homocysteine and improve the lipid profile and phytoestrogens to reduce the symptoms of menopause, as well as to help in the prevention of osteoporosis, breast cancer and CHD. Furthermore, the amount of each nutrient present varies according to the life stage for which the composition is targeted.

Detailed Description Text (11):
Vitamin B.sub.12, vitamin B.sub.6 and folic acid are included in each of the life stage specific dietary supplements of this invention. These elements act synergistically to reduce serum homocysteine, high levels of which are associated with coronary heart disease. Am. J. Clin. Nutr., 1992, 55:131-138; New Eng. J. Med., 1992, 32:1832-1835; Am J. Clin. Nutr., 1989, 50:353-358. The amount of folic acid in the three dietary supplements of this invention is maintained at about the same level in all three compositions, since folic acid not only reduces the risk of fetal neural tube defects, but, as noted above, also has been shown to have beneficial cardiac effects and to decrease the risk of cervical dysplasia. Scand. J. Clin. Lab Invest., 1988, 48:215-221. On the other hand, larger doses of vitamin B.sub.6 are included in the Stage I and Stage II formulations, as compared to Stage III, to assist in alleviating PMS symptoms. J. Royal Coll. Gen. Prac., 1989, 39:364-368; Obstetrics and Gyn., 1987, 70:147-149.

Detailed Description Text (15):
The dose of iron is highest in the Stage I dietary supplement of this invention and lowest in the Stage III dietary supplement, because iron deficiency anemia is a major health concern of menstruating women (Stage I and part of Stage II). Vitamin B.sub.12 deficiency results in pernicious anemia. Because this condition can be clinically masked if folate is provided in the diet without vitamin B.sub.12, all formulations of this invention contain both folic acid and Vitamin B.sub.12.

Detailed Description Text (16):
Stage I compositions also contain an amount of vitamin B.sub.6 sufficient to reduce symptoms of PMS and to compensate for reduced levels of this vitamin caused by oral contraceptive use. The amount of folic acid contained in the Stage I nutritional supplement is sufficient to prevent fetal neural tube defects during pregnancy, as well as to reduce the risk of cardiovascular disease by maintaining low homocysteine levels. It also reduces the risk of cervical dysplasia.

Detailed Description Text (17):
Thus, the Stage I dietary supplement contains an amount of vitamin B.sub.6 sufficient to reduce the effects of PMS, an amount of folic acid sufficient to prevent fetal neural tube defects and provide cardiac benefit, a sufficient amount of vitamin B.sub.12 to act in concert with vitamin B.sub.6 and folic acid present in the composition to reduce the levels of serum homocysteine, a sufficient amount of chromium to enhance glucose and lipid metabolism, antioxidants to help prevent CHD and some cancers, and calcium, together with a combination of other nutrients known to enhance its absorption and/or utilization to prevent osteoporosis, and an amount of phytoestrogens to beneficially modulate menses and provide protection against osteoporosis, some cancers and CHD. The Stage I dietary supplement is therefore particularly suited to meet the needs and address the health risks of a young adult female, while also lessening the risk of osteoporosis, cancer and coronary heart disease occurring in later life.

Detailed Description Text (21):
Optionally, the dietary supplements of this invention may further contain an amount of vitamin A or mixed carotenoids sufficient to supplement the nutritional needs of a woman at a particular lifestage. Vitamin A may be provided as preformed vitamin A or as mixed carotenoids, or both. There are more than 500 naturally occurring carotenoids, about 50 of which can serve as precursors of retinol and therefore have provitamin A activity. These include alpha- and beta-carotene and cryptoxanthin. However, non provitamin A carotenoids, such as lutein and lycopene have also been shown to have beneficial effects and may also be provided. Lycopene intake, for example, has been inversely associated with the risk of cervical cancer. Nutr & Cancer 1994, 21:193-201; Internat J. Cancer 1991; 48:34-8.

Detailed Description Text (30):
The dietary supplement for pre-perimenopausal women includes from about 200 to about 500 mg calcium, preferably from about 200 to about 300 mg calcium, and most preferably about 200 mg calcium; from about 100 to about 200 mg magnesium, preferably from about 100 to about 150 mg magnesium, and most preferably about 100 mg magnesium; from about 0.5 to about 1.5 mg boron, preferably about 0.7 to about 1.3 mg boron, and most preferably about 1 mg boron; from about 0.5 to about 1.5 mg copper, preferably about 0.7 to about 1.3 mg copper, and most preferably about 1 mg copper; from about 2 to about 2.6 mg manganese, preferably about 2 to about 2.4 mg manganese, and most preferably about 2 mg manganese; from about 10 to about 13 mg zinc, preferably about 10 to about 12 mg zinc, and most preferably about 10 mg zinc; from about 200 to about 300 IU vitamin D, preferably about 200 to about 250 IU vitamin D, and most preferably about 200 IU vitamin D; from about 12 to about 18 mg iron, preferably about 16 to about 18 mg iron, and most preferably about 18 mg iron; from about 400 to about 440 .mu.g folic acid, preferably about 400 to about 420 .mu.g folic acid, and most preferably about 400 .mu.g folic acid; from about 2 to about 10 .mu.g vitamin B.sub.12, preferably about 2 to about 4 .mu.g vitamin B.sub.12, and most preferably about 2 .mu.g vitamin B.sub.12 ; from about 50 to about 100 mg vitamin B.sub.6, preferably about 50 to about 65 mg vitamin B.sub.6, and most preferably about 50 mg vitamin B.sub.6 ; from about 50 to about 100 .mu.g chromium, preferably about 50 to about 75 .mu.g chromium, and most preferably about 50 .mu.g chromium; from about 100 to about 200 IU vitamin E, preferably about 100 to about 150 IU vitamin E, and most preferably about 100 IU vitamin E; from about 100 to about 1000 mg vitamin C, preferably about 100 to about 150 mg vitamin C, and most preferably about 100 mg vitamin C; and from about 8 to less than 50 mg phytoestrogen, preferably about 8 to about 12 mg phytoestrogen, and most preferably about 10 mg phytoestrogen.

Detailed Description Text (31):
This range of folic acid has been shown to be effective in preventing fetal neural tube defects and reducing the risk of cervical dysplasia; the amount of vitamin B.sub.6 is sufficient to reduce at least some symptoms of PMS; the amounts of vitamin B.sub.12, vitamin B.sub.6 and folic acid have been shown to reduce serum homocysteine; the amount of iron present in the composition is sufficient to reduce or prevent iron deficiency anemia; and phytoestrogen, antioxidants and chromium help reduce the risk of cardiovascular disease. Antioxidants and phytoestrogens also provide some protection against osteoporosis and some cancers.

Detailed Description Text (34):
The dietary supplement for perimenopausal and menopausal women includes from about 200 to about 1000 mg calcium, preferably from about 300 to about 400 mg calcium, and most preferably about 300 mg calcium; from about 100 to about 200 mg magnesium, preferably

from about 100 to about 150 mg magnesium, and most preferably about 150 mg magnesium; from about 1.5 to about 2.5 mg boron, preferably about 1.7 to about 2.3 mg boron, and most preferably about 2 mg boron; from about 1.5 to about 2.5 mg copper, preferably about 1.7 to about 2.3 mg copper, and most preferably about 2 mg copper; from about 2.4 to about 3.6 mg manganese, preferably about 2.6 to about 3.4 mg manganese, and most preferably about 3 mg manganese; from about 12 to about 15 mg zinc, preferably about 12 to about 14 mg zinc, and most preferably about 12 mg zinc; from about 300 to about 400 IU vitamin D, preferably about 300 to about 350 IU vitamin D, and most preferably about 300 IU vitamin D; from about 10 to about 15 mg iron, preferably about 13 to 15 mg iron, and most preferably about 15 mg iron; from about 400 to about 440 .mu.g folic acid, preferably about 400 to about 420 .mu.g folic acid, and most preferably about 400 .mu.g folic acid; from about 2 to about 15 .mu.g vitamin B.sub.12, preferably about 2 to about 6 .mu.g vitamin B.sub.12, and most preferably about 2 .mu.g B.sub.12, from about 50 to about 100 mg vitamin B.sub.6, preferably about 50 to about 65 mg vitamin B.sub.6, and most preferably about 50 mg vitamin B.sub.6 ; from about 75 to about 200 .mu.g chromium, preferably about 75 to about 100 .mu.g chromium, and most preferably about 75 .mu.g chromium; from about 200 to about 400 IU vitamin E, preferably about 200 to about 300 IU vitamin E, and most preferably about 200 IU vitamin E; from about 200 to about 1000 mg vitamin C, preferably about 200 to about 300 mg vitamin C, and most preferably about 200 mg Vitamin C; and from about 10 to less than 50 mg phytoestrogen, preferably about 12 to about 17 mg phytoestrogen, and most preferably 15 mg phytoestrogen.

Detailed Description Text (35):
The amount of calcium, magnesium, boron, copper, manganese, zinc and vitamin D in the Stage II composition has been increased in comparison to the Stage I composition since these nutrients have been shown to enhance calcium absorption and/or utilization; the amount of vitamin B.sub.6 is the same as in the Stage I composition and is sufficient to prevent or reduce symptoms of PMS; the amounts of folic acid will prevent fetal neural tube defects and reduce the risk of cervical dysplasia, and in combination with vitamin B.sub.12 and vitamin B.sub.6 is associated with a reduced risk of CHD; chromium has also been increased to help regulate the lipid profile and thereby reduce the risk of CHD; the amount of phytoestrogen contributes to the reduction of menopausal symptoms, osteoporosis, CHD and some forms of cancer, and therefore is increased in the composition for the second life stage. Similarly, the amount of antioxidants are increased in the Stage II composition because they also provide protection against CHD and some cancers.

Detailed Description Text (38):
The dietary supplement for post-menopausal women includes from about 200 to about 1500 mg calcium, preferably from about 300 to about 500 mg calcium, and most preferably about 400 mg calcium; from about 150 to about 250 mg magnesium, preferably from about 150 to about 200 mg magnesium, and most preferably about 200 mg magnesium; from about 2.5 to about 3.5 mg boron, preferably about 2.7 to about 3.3 mg boron, and most preferably about 3 mg boron; from about 2.5 to about 3.5 mg copper, preferably about 2.7 to about 3.3 mg copper, and most preferably about 3 mg copper; from about 4.4 to about 5.6 mg manganese, preferably about 4.6 to about 5.4 mg manganese, and most preferably about 5.0 mg manganese; from about 15 to about 18 mg zinc, preferably about 15 to about 17 mg zinc, and most preferably about 15 mg zinc; from about 300 to about 800 IU vitamin D, preferably about 350 to about 400 IU vitamin D, and most preferably about 400 IU vitamin D; from about 5 to about 10 mg iron, preferably about 8 to 10 mg iron, and most preferably about 10 mg iron; from about 400 to about 440 .mu.g folic acid, preferably about 400 to about 420 .mu.g folic acid, and most preferably about 400 .mu.g folic acid; from about 2 to about 18 .mu.g vitamin B.sub.12, preferably about 2 to about 8 .mu.g vitamin B.sub.12, and most preferably about 2 .mu.g vitamin B.sub.12 ; from about 1.6 to about 10 mg vitamin B.sub.6, preferably about 1.6 to 3.2 mg vitamin B.sub.6, most preferably about 1.6 mg vitamin B.sub.6 ; from about 100 to about 200 .mu.g chromium, preferably about 100 to about 150 .mu.g chromium, and most preferably about 100 .mu.g chromium; from about 350 to about 800 IU vitamin E, preferably about 350 to about 450 IU vitamin E, and most preferably about 400 IU vitamin E; from about 300 to about 1000 mg vitamin C, preferably about 350 to about 450 mg vitamin C, and most preferably about 400 mg vitamin C; and from about 10 to less than 50 mg phytoestrogen, preferably about 12 to about 17 mg phytoestrogen, and most preferably about 15 mg phytoestrogen.

Detailed Description Text (39):
The amounts of calcium, manganese, boron, copper, magnesium, zinc and vitamin D are optimized to enhance calcium uptake and/or utilization for the prevention of osteoporotic fractures; the amounts of antioxidant, vitamin B.sub.12, vitamin B.sub.6, folic acid, and chromium are maximized to prevent or reduce the risk of CHD;

phytoestrogens and antioxidants contribute to reducing the risk of cardiovascular disease and some cancers.

Detailed Description Text (45):
The present method for preventing or lessening the risk of life stage associated health conditions is effective in the prevention of fetal neural tube defects, prevention or reduction of symptoms of PMS and menopause, prevention or reduction of the risk of developing osteoporosis, iron deficiency anemia, coronary heart disease, some cancers and cervical dysplasia.

Detailed Description Paragraph Table (1):
TABLE I DIETARY SUPPLEMENTS COMPONENT STAGE I STAGE II STAGE III Calcium 200 mg 300 mg 400 mg Magnesium mg00 mg50 200 mg Boron mg 1 mg 2 mg Copper mg 1 mg 2 mg Manganese mg 2 mg3 5 mg Zinc mg 10 mg12 15 mg Vitamin D IU00 IU00 400 IU Iron mg 18 mg5 10 mg Folic Acid 400 .mu.g 400 .mu.g 400 .mu.g Vitamin B12 .mu.g 2 .mu.g 2 .mu.g Vitamin B6 mg0 mg50 1.6 mg Chromium .mu.g 75 .mu.g 100 .mu.g Vitamin E IU00 IU00 400 IU Vitarnin C 100 mg mg00 400 mg Phytoestrogen 10 mg mg15 15 mg

Other Reference Publication (6):
Butterworth, et al., Folic Acid Safety and Toxicity: . . . , Am J Clin Nutr, vol. 50, pp. 353-358, 1989.

Other Reference Publication (7):
Bailey, Ph.D., L.B., Evaluation of A New Recommended Dietary Allowance for Folate, J Amer Dietetic Assn, vol. 92, pp. 463-468, 1992.

Other Reference Publication (8):
Butterworth, et al., Improvement in Cervical Dysplasia . . . , The Amer Jour of Clin Nutr, vol. 35, pp. 73-82, 1982.

Other Reference Publication (10):
Brattstrom, et al., Folic Acid--An Innocuous Means to Reduce Plasma Homocysteine, Scand J Clin Lab Invest, vol. 48, pp. 215-221, 1988.

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L7: Entry 127 of 146 File: USPT Aug 14, 2001

US-PAT-NO: 6274564
DOCUMENT-IDENTIFIER: US 6274564 B1

TITLE: Compositions of cobalamin and related corrinoids, and uses thereof

DATE-ISSUED: August 14, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sarill; William J.	Arlington	MA	02154	
Brennan; Thomas F.	Nyack	NY	10960	

APPL-NO: 08/ 936781 [PALM]
DATE FILED: September 17, 1997

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This applications claims benefit under 35 U.S.C. 119(e) to co-pending U.S. provisional applications Ser. No. 60/025,298, filed Sep. 18, 1996, and Ser. No. 60/041,750, filed Mar. 28, 1997; the contents of which are hereby incorporated by reference.

INT-CL: [07] A61 K 31/70, A61 K 31/195

US-CL-ISSUED: 514/52; 514/561, 514/563, 514/567
US-CL-CURRENT: 514/52; 514/561, 514/563, 514/567

FIELD-OF-SEARCH: 514/52, 514/561, 514/563, 514/567

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5039668	August 1991	Colina	514/52
☐	5716941	February 1998	Rabinoff	514/52

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
1345327	January 1994	EP	
48021484	July 1965	JP	
WO 98/19690	May 1998	WO	

OTHER PUBLICATIONS

Matera, et al. "Pharmacokinetic Study of the Relative Bioavailability and Bioequivalence After Oral Intensive or Repeated Short Term Treatment with Two Polyamino Acid Formulations" Int. J. Clin. Pharm. Res. XIII(2) 93-105 (1993).
Dekoninck et al 94 CA 154479R, 1981.*
Basun et al 115 CA 156375e, 1991.*
Nadeau et al 110 CA 153177c, 1989.

ART-UNIT: 167

PRIMARY-EXAMINER: Travers; Russell

ABSTRACT:

Novel compositions cobalamin and related corrinoids, and uses thereof, are disclosed. The novel compositions include a corrin, a first amino acid having a side chain which includes a basic or positively charged moiety; and a second amino acid with an uncharged side chain which includes at least one heteroatom. The compositions are useful for, inter alia, treatment of cobalamin deficiency.

17 Claims, 0 Drawing figures

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L12: Entry 128 of 210 File: USPT Apr 23, 2002

US-PAT-NO: 6375956
DOCUMENT-IDENTIFIER: US 6375956 B1

TITLE: Strip pack

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hermelin; Marc S.	Glendale	MO		
Kirschner; Mitchell I.	St. Louis	MO		
Osinga; Sjoerd	Ellisville	MO		

US-CL-CURRENT: 424/400; 206/528, 206/531, 206/534, 206/538, 424/441, 424/456, 424/464, 424/466, 424/489

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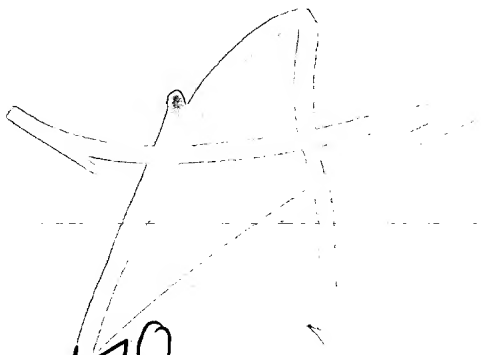

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Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L1	tramadol and aspirin	149	L1
L2	tramadol and aspirin and molar	50	L2
L3	folic or folate or polyglutamate	8276	L3
L4	(folic or folate or polyglutamate)and hpv	89	L4
L5	(folic or folate or polyglutamate)and hpv and contraceptive	6	L5
L6	(folic or folate or polyglutamate) and contraceptive	286	L6
L7	(cervical or cervix or dysplasia) and (folic or folate or polyglutamate) and contraceptive	146	L7
L8	polypepetide and signal and protease and recognition and target	16	L8
L9	polypeptide and signal and (protease adj recognition) and target	257	L9
L10	(polypeptide adj signal) and (protease adj recognition) and target and recombinant	4	L10
L11	vitamins and contraceptive	1156	L11
L12	folic and vitamins and contraceptive	210	L12

END OF SEARCH HISTORY

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L7: Entry 135 of 146 File: USPT Dec 21, 1999

DOCUMENT-IDENTIFIER: US 6004582 A
TITLE: Multi-layered osmotic device

Brief Summary Text (20):
Different environments for use of the osmotic device include biological environments such as the oral, ocular, nasal, vaginal, glands, gastrointestinal tract, rectum, cervical, intrauterine, arterial, venous, otic, sublingual, dermal, epidermal, subdermal, implant, buccal, bioadhesive, mucosal and other similar environments. Likewise, it may be used in aquariums, industrial warehouses, laboratory facilities, hospitals, chemical reactions and other facilities.

Detailed Description Text (46):
Further therapeutic compounds which can be formulated into the present osmotic devices also include antibacterial substances, antihistamines and decongestants, anti-inflammatories, antiparasitics, antivirals, local anesthetics, antifungal, amoebicidal, or trichomonocidal agents, analgesics, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, neuroleptics, antihypertensives, muscle relaxants, depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anti-convulsants, antiparkinson agents, muscle contractants, anti-microbials, antimalarials, hormonal agents, contraceptives, sympathomimetics, diuretics, hypoglycemics, ophthalmics, electrolytes, diagnostics agents and cardiovascular drugs.

Detailed Description Text (72):
Representative nutritional agents are ascorbic acid, niacin, nicotinamide, folic acid, choline biotin, panthothenic acid, and vitamin B.sub.12, essential amino acids; essential fats.

Detailed Description Text (78):
As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B12, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof Coenzymes are specific chemical forms of vitamins and can include thiamine pyrophosphates (TPP), flavin mononucleotide (FMN), flavin adenine dinucleotive (FAD), Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Coenzyme A (CoA), pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B12, lipoyllysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, carnitine, and alpha, beta, and gamma carotenes.

L7: Entry 124 of 146 File: USPT Mar 5, 2002

DOCUMENT-IDENTIFIER: US 6352721 B1
TITLE: Combined diffusion/osmotic pumping drug delivery system

Brief Summary Text (28):
Other preferred embodiments of the device of the invention are used in biological environments including the oral, ocular, nasal, vaginal, glandular, gastrointestinal tract, rectal, cervical, intrauterine, arterial, venous, otic, sublingual, dermal, epidermal, subdermal, implant, buccal, bioadhesive, mucosal and other similar environments. Likewise, it may be used in aquariums, industrial warehouses, laboratory facilities, hospitals, chemical reactions and other facilities.

Detailed Description Text (50):
When the active agent is a therapeutic compound, exemplary therapeutic compounds include antibiotics, antihistamines and decongestants, antiinflammatory agents, antiparasitics, antivirals, local anesthetics, antifungal agents, amoebicidal agents, trichomonocidal agents, analgesics, antiarthrits agents, anthiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, neuroleptics, antihypertensives, antidepressants, hypnotics, sedatives, anxyolitic energizers, anti-convulsants, antiparkinson agents, muscle relaxant agents, antimalarials, hormonal agents, contraceptives, sympathomimetics, diuretics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents and cardiovascular drugs.

Detailed Description Text (54):
Representative antineoplastics include nitrogen mustards such as mechlorethamine chlorambucil, cyclophosphamide; ethylenimines and methylmelamines such as triethylenemelamine, thiotepa, hexamethyl-melamine; alkyl sulfonates such as busulfan; nitrosureas such as carmustine (BCNU), lomustine; dacarbazine; folic acid analogs such as methotrexate; pyrimidine analogs such as fluorouracil, arabinoside cytisine; purine analogs such as mercaptopurine, azathiprine; vinca alkaloids such as vincristine, vinblastine, taxol; etoposide; antibiotics such as actinomycin D, daunorubicin, doxorubicin, bleomycin, mitomycin; cisplatin; hydroxyurea; procarbazine; aminoglutethimide; cisplatin and tamoxifen.

Detailed Description Text (74):
Representative nutritional agents include ascorbic acid, niacin, nicotinamide, folic acid, choline biotin, panthothenic acid, and vitamin B12, essential amino acids, and essential fats.

Detailed Description Text (79):
As used in this disclosure, the term vitamin refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term vitamin(s) include, without limitation, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B12, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term vitamin are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins and can include thiamin pyrophosphates (TPP), flavin mononucleotide (FMN), and flavin adenine dinucleotive (FAD). Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Coenzyme A (CoA), pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B12, lipolysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term vitamin(s) also includes choline, camitine, and alpha, beta, and gamma carotene.

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L7: Entry 124 of 146 File: USPT Mar 5, 2002

US-PAT-NO: 6352721
DOCUMENT-IDENTIFIER: US 6352721 B1

TITLE: Combined diffusion/osmotic pumping drug delivery system

DATE-ISSUED: March 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Osmotica Corp.	Tortola			VG	03

APPL-NO: 09/ 483282 [PALM]
DATE FILED: January 14, 2000

INT-CL: [07] A61 K 9/22, A61 K 9/24, A61 K 9/44

US-CL-ISSUED: 424/473; 424/468, 424/472, 424/422, 424/423, 424/424, 424/427, 424/435, 424/436, 424/437, 514/772.3, 514/781, 514/784, 514/785, 514/786
US-CL-CURRENT: 424/473; 424/422, 424/423, 424/424, 424/427, 424/435, 424/436, 424/437, 424/468, 424/472, 514/772.3, 514/781, 514/784, 514/785, 514/786

FIELD-OF-SEARCH: 424/464, 424/465, 424/468, 424/471, 424/472, 424/473, 424/474, 424/475, 424/479, 424/480, 424/467, 424/422, 424/423, 424/424, 424/427, 424/435, 424/436, 424/437

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4235236	November 1980	Theeuwes	
☐	4693886	September 1987	Ayer	
☐	4765989	August 1988	Wong et al.	
☐	4859470	August 1989	Guittard et al.	
☐	4968507	November 1990	Zentner et al.	
☐	5004614	April 1991	Staniforth	
☐	5516527	May 1996	Curatolo	
☐	5543155	August 1996	Fekete et al.	

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
1 027 888	August 2000	EP	
2074860	February 1984	GB	

OTHER PUBLICATIONS

The Physicians'Desk Reference (Medical Economics Company, Inc. 1998) monograph for Allegra-D.

ART-UNIT: 1615

PRIMARY-EXAMINER: Spear; James M.

ABSTRACT:

Delivery devices capable of delivering one or more active substances by diffusion through plural micropores in the membrane or by osmotic pumping through one or more preformed passageways in the membrane are provided. The device has an about centrally located expandable core completely surrounded by an active substance-containing layer, which is completely surrounded by the membrane. The device is capable of delivering insoluble, slightly soluble, sparingly soluble and very soluble active substances to an environment of use. The preferred delivery rate is zero order. The device can deliver an active substance for a period of about 12-24 hours.

37 Claims, 5 Drawing figures

L7: Entry 129 of 146 File: USPT Apr 10, 2001

DOCUMENT-IDENTIFIER: US 6214815 B1
TITLE: Triphasic oral contraceptive

Brief Summary Text (1):
The present invention relates to triphasic oral contraceptive regimens of steroids. More particularly, the present invention relates to a triphasic contraceptive regimen containing a progestin and low doses of ethinyl estradiol (EE).

Brief Summary Text (4):
In the past years, it has been recognized that there are certain benefits associated with steroid based oral contraceptives, i.e. OCs, having lower doses of progestin, and especially, lower doses of estrogen. Such benefits of lower estrogen doses include decreased incidence of nuisance side effects, such as, nausea, vomiting, and gastric upset, as well as a decreased incidence of serious side effects, such as, thromboembolism, stroke, and myocardial infarction. Thus, while the advantages of steroid based contraceptives are well established in the medical community, it is desirable to administer the lowest effective dose of steroids, on a patient by patient basis, in order to minimize these types of side effects.

Brief Summary Text (10):
Task Force on Oral Contraceptives--WHO Special Program of Research, Development, and Research Training in Human Reproduction; Contraception 1982; Vol. 25, Number 3, demonstrates that a combination of 1 mg norethindrone acetate and 50 .mu.g of EE has better cycle control than a combination of 1 mg norethindrone acetate and 20 .mu.g of EE.

Brief Summary Text (13):
Three-stage or triphasic combination type oral contraceptive regimens are known. Triphasic regimens of various types are described in U.S. Pat. Nos. 4,390,531; 4,066,757; 3,957,982; 3,795,734; and 2,431,704.

Brief Summary Text (14):
More recently, Pasquale S., U.S. Pat. Nos. 4,530,839; 4,544,554; 4,616,006; and 4,628,051 described a triphasic regimen of contraception which comprises administering for 21 successive days to a female of childbearing age a combination of an estrogen and a progestogen in a low but contraceptively effective daily dosage corresponding in estrogenic activity to 20-50 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity to 0.065-0.75 mg of norethindrone for 5-8 days; for the next 7-11 days an estrogen daily dosage equal to 20-50 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity to 0.250-1.0 mg of norethindrone; and for the next 3-7 days an estrogen daily dosage equal to 20-50 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity 0.35-2.0 mg of norethindrone; followed by 6-8 days without estrogen and progestogen administration, provided that the estrogen daily dosage is the same for each period. The purpose of this regimen is to lower the total monthly steroid dose in the oral contraceptive while still obtaining equivalent bleeding patterns and protection against pregnancy as found with conventional oral contraceptives.

Brief Summary Text (16):
There is a need, however, for a combination type contraceptive which contains even lower total monthly steroid doses, particularly of estrogen, yet is still effective for the prevention of pregnancy and maintains a high level of cycle control.

Brief Summary Text (22):
The total number of days during which the progestogen and estrogen combinations are administered daily is preferably 21. These are followed by 4-8 days which are free of

hormone administration to approximate the natural 28-day menstrual cycle of the female. Day one of the cycle is defined as the first day of menstruation and the days are numbered sequentially thereafter until menstruation occurs again. The cycle usually lasts 28 days but it may be slightly longer or shorter. In actual practice, the placebo or any of the hormone containing tablets might contain nutritional supplements such as, for example, iron supplements, folic acid, calcium, etc. Thus, in a preferred regimen, phase one would commence sometime between day 1 and day 7 of the menstrual cycle and last 5-8 days but preferably 7 days, phase two would last 7-11 days, preferably 7 days, while phase three would last 3 to 7 days, preferably 7 days.

Brief Summary Text (23):
The contraceptive composition employed in the present invention comprises separate daily dosage units which are adapted for successive daily oral ingestion. The composition consists essentially of, as the first phase, 5-8 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen in combination with a progestogen, followed by, as the second phase, 7-11 dosage units containing, a combination of estrogen and a progestogen, followed by, as the third phase, 3-7 dosage units containing a combination of an estrogen and a progestogen optionally followed by 48 dosage units free of estrogen and progestogen. The estrogen daily dosage is kept constant in all three phases.

Brief Summary Text (24):
Any conventional estrogen may be employed as a suitable component in the contraceptive regimen of this invention. The particular regimen employed in a daily dosage should be equal in contraceptive activity in each phase to a daily dosage of about 23-28 .mu.g of 17.alpha.-ethinylestradiol. The preferred dosage is one equal to a daily dosage of about 25 .mu.g of 17.alpha.-ethinylestradiol.

Brief Summary Text (31):
In the case of the preferred oral application, the three-phase combination-type contraceptives are preferably packaged in the form of a pharmaceutical kit or package in which the daily dosages are arranged for proper sequential administration. This invention also relates, therefore, to a pharmaceutical unit which contains combination-type contraceptives in dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

Detailed Description Text (4):
A total of 649 healthy, sexually active women between 18 and 39 years of age, who required contraception for at least 12 months, were recruited for the study. The volunteers included both new users and women switching from another oral contraceptive. Women were excluded from the study if they had used parenteral depot-contraceptives during the last six months, had liver disease, vascular or metabolic diseases, tumors, pregnancy, diagnostically unclassified genital bleeding, and all other known contraindications for OC use. A desire for contraception over at least 12 months was essential. Women received strips of pills containing either 21 sugar-coated tables of the test preparation, which contained 20 .mu.g EE and 75 .mu.g GSD (SH D 543 A, Schering AG), or the reference preparation, which contained 21 tablets of 30 .mu.g EE and 75 .mu.g GSD (FEMODENE, SH D 356 C, Schering AG). Women started taking the study preparations on the first day of their next menstrual period.

Detailed Description Text (7):
In all, 428 cases with a total of 4470 cycles of treatment were evaluated for the oral contraceptive containing 20 .mu.g EE and 75 .mu.g GSD (SH D 543 A--test preparation, 20 .mu.g EE preparation) and 221 cases with a total of 2377 cycles were evaluated for the oral contraceptive containing 30 .mu.g EE and 75 .mu.g GSD (SH D 356 C--reference, 30 .mu.g EE preparation). A maximum of 12 cycles was included in all data analyses. A total of 74.6% of the subjects treated with the 20 .mu.g EE preparation and 76.6% of the women under the 30 .mu.g EE preparation completed 12 cycles of treatment. About 95% of the volunteers did not miss any pill during the study. A total of 5.1 % of women taking the 20 .mu.g EE preparation and 4.9% of the women taking the reference preparation (30 .mu.g EE) missed one or more pills in the course of the study.

Detailed Description Text (10):
The frequency of any intermenstrual bleeding (spotting as well as normal or excessive breakthrough bleeding) generally decreased under both preparations from the first three cycles to cycle 12 (Table 2). The highest incidence of spotting (spotting only) was reported by 22.6% of the subjects under the 20 .mu.g preparation (SH D 543 A) and by 13.8% of the subjects under the 30 .mu.g EE oral contraceptive (FEMONDENE) in the first

cycle (Table 2). The highest incidence of normal/excessive breakthrough bleeding (breakthrough bleeding only) was reported by 2.4% in the third 20 .mu.g EE cycle. Thereafter, the number of women with any type of intermenstrual bleeding declined continuously to low levels of less than 7% and 5%, respectively. The majority of women had fewer than two treatment cycles with breakthrough bleeding. The values reported in Table 2 were obtained by reading or estimating the value from bar charts in the original article.

Detailed Description Text (15):
Only women of fertile age, with regular cycle control and normally exposed to risk of pregnancy were admitted to the trials. Women who had used other contraceptives before, should have terminated their previous treatment at least 2 months before the start of the investigation and should have experienced at least two spontaneous menstrual periods. Women with any generally accepted contraindication for oral contraceptive use were excluded.

Detailed Description Text (16):
Of the 270 women who participated in the two trials, 91 used the oral contraceptive combination 0.150 mg desogestrel +30 .mu.g ethinylestradiol Marvelon.RTM.) for a total of 964 (treatment) cycles in one trial, while the other 179 women used the combination 0.150 mg desogestrel +20 .mu.g ethinylestradiol (Mercilon.RTM.) for a total of 2096 cycles in the other trial. Since the two trials were set up as separate studies, there was no randomization in the assignment of women to the two treatment groups. Both treatments are monophasic. Each treatment cycle consists of a period of 21 days of daily tablet intake (1 tablet per day) followed by a tablet-free period of 7 days.

Detailed Description Text (18):
Efficacy of both the 0.150/0.030 and the 0.150/0.020 mg desogestrel/EE combination was good. There were no pregnancies with either contraceptive combinations.

Detailed Description Text (22):
Oral contraceptives containing 0.150 mg desogestrel and 20 or 30 .mu.g of EE per tablet (Mercilon.RTM. and Marvelon.RTM./Desolett.RTM., respectively) were compared in 1000 women over a treatment period of one year as fully described by Akerlund, M.; A. Rode; and J. Westergaard; Brit J Obstet Gynecol September 1993; 100: 832-838. The sample size of the study (2.times.500 participants) was determined so that it would be possible to demonstrate that there was a minimal difference with respect to presence of irregular bleeding. The following is reported here for convenience and is incomplete as compared to the full text of the article.

Detailed Description Text (23):
Women asking for oral contraception were recruited for the study. In Norway 300 women were recruited for the study (six centres, all private gynaecological practics), in Sweden 500 women (two university clinics, two central hospitals, one private practice) and in Denmark 200 women (one university clinic). The participating women were aged 18 to 35 (Norway) or 18 to 40 years (Sweden, Denmark). The women were randomly allocated to the study medication according to a list provided by Organon International bv (Oss, The Netherlands): 485 women on the 150/20 .mu.g and 497 on the 150/30 .mu.g combination. The tablets were supplied by Organon International bv in standard, unmarked 21 day blister packs. Women either changed from another OC formulation to the study medication (switchers) or had not used any hormonal contraceptive medication for at least two months (starters).

Detailed Description Text (31):
There was conducted a randomized, multi-center study to evaluate three blinded regimens of norgestimate and ethinyl estradiol (NGM/EE) oral contraceptive and an open-label control regimen. One of these blinded regimens was a triphasic regimen embodying the present invention. In this triphasic regimen there was administered in the first phase a tablet containing 0.180 mg of norgestimate +25 .mu.g EE once a day for 7 days; in the second phase a tablet containing 0.215 mg of norgestimate +25 .mu.g EE once a day for 7 days; and in the third phase a tablet containing 0.250 mg of norgestimate +25 .mu.g EE; followed by 7 days of placebo tablets. Approximately 6300 subjects were enrolled in the full study. The ratio of subjects assigned to each of the three blinded regimen groups versus the open label control regimen group was 3:2. The first 500 subjects in each of the three blinded regimen groups were expected to complete 13 cycles. All other subjects were enrolled for 6 cycles. An Interactive Voice Randomization System (IVRS) was used to randomize subjects into the study.

Detailed Description Text (49):

have no current evidence of cervical dysplasia.

Detailed Description Text (53):
history or presence of disorders commonly accepted as contraindications to combined oral contraceptives, including but not limited to the following:

Detailed Description Text (56):
a benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen containing products

Detailed Description Text (61):
presence of disorders commonly accepted as contraindications to oral contraceptives, including but not limited to the following:

Detailed Description Text (73):
At the pre-study visit, a complete medical history with emphasis on menstrual history and use of hormonal contraceptives, was obtained for each subject. In addition, a complete physical and gynecologic examination, including vital signs, breast and pelvic exam, was conducted. A Papanicolaou (PAP) smear was done, although a smear done within 2 months with a report available prior to study entry was acceptable. An assessment of body mass index was also accomplished. At the admission visit, subjects returned in a fasted state for a hematology profile, clinical chemistries, urine dipstick and a .beta.-subunit HCG RIA pregnancy test. Subjects randomized to the three blinded regimen groups began taking study medication on the first day of the menstrual cycle. Subjects were seen for follow-up visits at the end of cycles 1, 3, 6, 9 and 13. At each visit, vital signs were obtained and the diary cards and study drug packs were reviewed. At the cycle 6 and cycle 13 visits, blood was drawn for a hematology profile and clinical chemistries. Subjects who did not have onset of menses during the placebo tablet days of any cycle were to immediately contact the investigator and have a subunit HCG RIA performed. The following medications were not permitted during the study, as they would confound the effects of the study drug: steroid hormonal therapy, barbiturates, antiepileptics, rifampin, griseofulvin, and other hepatic enzyme inducers.

Detailed Description Text (79):
In an earlier and different study that that conducted in Example 1, there was conducted a randomized, multi-centered, single-cell Phase III study to evaluate a triphasic regimen of norgestimate and ethinyl estradiol (NGM/EE) oral contraceptive. In this triphasic regimen there was administered in the first phase a tablet containing 0.180 mg of norgestimate +35 .mu.g EE once a day for 7 days; in the second phase a tablet containig 0.215 mg of norgestimate +35 .mu.g EE once a day for 7 days; and in the third phase a tablet containing 0.250 mg of norgestimate +35 .mu.g EE; followed by 7 days of placebo tablets. All investigators used a common protocol and case record forms. Each investigator was to enroll a block of 50 subjects for a total of 1800 subjects. Investigators were selected on the basis of their experience in family planning. Investigator sites were selected to include regions throughout the United States in clinic and private settings, in order to reduce demographic bias. Each subject was expected to complete 24 consecutive cycles of therapy and be involved in the study for a maximum of 28 months (including post-therapy follow-up).

Detailed Description Text (80):
To be admitted to the study, each woman had to meet the inclusion criteria and exhibit none of the exclusion characteristics including contraindications to oral contraceptive use.

Detailed Description Text (87):
6. have a Papanicolaou smear with no evidence of dysplasia

Detailed Description Text (97):
7. benign or malignant liver tumor which developed during the use of oral contraceptives or other estrogen-containing products

Other Reference Publication (1):
Schwarz B E Et Al: "Reference period analysis of vaginal bleeding with triphasic oral contraceptive agents containing norethindrone or levonorgestrel: a comparison study." International Journal of Fertility, (1992 May-Jun.) 37 (3) 176-82, XP000881622 pp. 176-177, p. 178; table 1 p. 181.

Other Reference Publication (2):
Lox C D: "Biochemical effects in women following one year's exposure to a new triphasic

contraceptive-I. Chemistry profiles." General Pharmacology, (Mar. 1996 27 (2) 367-70., XP000881634 p. 367.

Other Reference Publication (3):
A twelve-month Comparative Clinical Investigation of Two Low-Dose Oral Contraceptives Containing 20 ug Ethinylestradiol/75 ug Gestodene and 30 ug Ethinylestradiol/75 ug Gestodene With Respect to Efficacy, Cycle Control, and Tolerance, Endrilkat, J., U. Muller, and B. Dusterberg, Contaception 1977; 55: 131-137.

Other Reference Publication (4):
Investigation of the Influence of Two Low-dose Monophasic Oral Contraceptives Containing 20 ug Ethinylestradiol/75 ug Gestodene and 30 ug Ethinylestradiol/75 ug on Lipid Metabolism in an Open Randomized Trial, Brill, K., A. Then, U Beisiegel, A. Jene, C. Wunsch, and F. Leidenberger, Contraception 1996; 54: 291-291.

Other Reference Publication (5):
A Clinical Comparison in Finland of Two Oral Contraceptives containing 0.150 mg Desogestrel in Combination with 0.020 mg or 0.030 mg Ethinylestradiol, Acta Obstet Gynecol Scand Suppl 1987; 144: 7-12, Tuimala, R., M. Saranen, and U. Alapiessa.

Other Reference Publication (6):
Oral Contraceptive Tablets Containing 20 and 30 Ug of Ethinyl Estradiol with 150 ug Desogestrel, Aceta Obstet Gynecol Scand 1994; 73: 136-143, Akerlund, M., E. Almstrom, S.Hogsted, and M. Nabrink.

Other Reference Publication (7):
Comparative Profiles of Reliability, Cycle Control, and Side Effects of Two Oral Contraceptive Formulations Containing 150 ug Desogestrel and Either 30 ug or 20 ug Ethinyl Estradiol, British Journal of Obstetrics and Gynaecology Sep. 1993, vol. 100, pp. 832-838, Akerlund, M., A. Rode, and J. Westergaard.

Other Reference Publication (9):
Hemostatic and Metabolic Effects of Lowering the Ethinyl Estradiol Dose From 30 mcg to 20 mcg in Oral Contraceptives Containing Desogestrel, Contraception 1993: 48, Sep., Basdevant, A, J. Contrad, C. Pelissier, et al.

Other Reference Publication (10):
A Randomized Double-Blind Study of Six Combined Oral Contraceptives, Contraception 1982 Vol. 25, No. 3, Task Force on Oral Contraceptives-WHO Special Program of Research, Development, and Research Training in Human Reproduction, pp. 231-241.

Other Reference Publication (12):
Effect of Oral Contraceptives Containing 20 and 35 ug Ethinyl Estradiol on Urinary Prostacyclin and Thromboxane Levels in Smokers and Non-Smokers, Susan Pioszal, MD, Melvin H. Thornton MD, Frank Z. Stanczyk PhD, Daniel R. Mishell, Jr., MD, Dept of Ob/Gyn, University of Southern California School of Medicine, Los Angeles, CA (1998), P. 60.

Other Reference Publication (13):
Changes in Androgens During Treatment with Four Low-Dose Contraceptives, C.M.H. Coenen, C.M.G. Thomas, G.F. Borm, J.M.G. Hollanders, and R. Rolland, Contraception 1996; 53: 171-176.

CLAIMS:

2. A triphasic oral contraceptive unit having 21 separate dosage units, adapted for successive daily oral administration comprising: 5-8 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen and a progestogen at contraceptively effective dosages corresponding in estrogenic activity to 25 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity to 0.180 mg of norgestimate as a first phase; followed by 7-11 dosage units containing in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen and a progestagen at a contraceptively effective dosage corresponding in estrogenic activity to 25 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity to 0.215 mg of norgestimate as a second phase; followed by 3-7 dosage units containing in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen at a contraceptively effective dosage corresponding in estrogenic activity to 25 .mu.g of 17.alpha.-ethinylestradiol and in progestogenic activity to 0.250 mg of norgestimate as a third phase; and optionally containing 4-8 additional dosage units free of estrogen

and progestogen.

4. A triphasic oral contraceptive unit having 21 separate dosage units, adapted for successive daily oral administration comprising: 7 dosage units containing in admixture with a pharmaceutically acceptable carrier, 25 .mu.g of 17.alpha.-ethinylestradiol and 0.180 mg of norgestimate, 7 dosage units containing in admixture with a pharmaceutically acceptable carrier, 25 .mu.g of 17.alpha.-ethinylestradiol and 0.215 mg of norgestimate; and 7 dosage units containing in admixture with a pharmaceutically acceptable carrier, 25 .mu.g of 17.alpha.-ethinylestradiol and 0.250 mg of norgestimate; and optionally containing 7 additional dosage units free of estrogen and progestogen.

L7: Entry 126 of 146 File: USPT Nov 20, 2001

DOCUMENT-IDENTIFIER: US 6319951 B1
TITLE: Use of 3-amino-4-hydroxybenzoic acid for the treatment of retroviral infections

Abstract Text (1):
3-amino-4-hydroxybenzoic acid or a derivative thereof is used in the preparation of a medicament for treating retroviral infections and HIV in particular. The 3-amino-4-hydroxybenzoic acid or a derivative thereof is also included in a pharmaceutical composition in combination with a pharmaceutically acceptable carrier and any of vitamin B.sub.12, folic acid, vitamin C or a combination of two or more thereof.

Brief Summary Text (31):
Synthesis of RNA and DNA by the virus using the host biochemistry consumes a lot of vitamin B.sub.12, folic acid and vitamin C. Depletion of B.sub.12 has been found to be a uniform finding in all AIDS cases.

Brief Summary Text (39):
The compound has previously been used orally as a Maillard reaction inhibitor as disclosed in European Patent 0474874 for treatment of diabetes mellitus. It has also been used as an active ingredient in vaginal contraceptive formulations where it was erroneously thought to be spermicidal when in actuality it inactivates an achrosomal proteolytic enzyme hyaluronidase essential for sperms to penetrate to the ovum. For the last 25 years 3-amino-4-hydroxybenzoic acid has also been in use along with other compounds such as tartaric acid, citric acid, sodium bicarbonate and sodium carbonate as a spermicidal foaming tablet. The foam from the tablet blocks the entrance to the cervix for the sperms, making fertilization difficult. The bubbles create surface tension forces which immobilize sperms so that they do not reach the ovum for fertilization. The soluble sodium carbonate reacts with calcium ions in semen to form the insoluble calcium carbonate (chalk) which arrests sperm (as though they were swimming in mud) and also blocks the entrance to the uterus so that the sperms cannot reach the ovum for fertilization. Should sperms find their way to the ovum they fail to penetrate the coating of the ovum called zona pellucida because, the 3-amino-4-hydroxybenzoic acid inactivates the proteolytic enzyme necessary for digesting the way through the zona pellucida.

Brief Summary Text (43):
The active ingredient 3-amino-4-hydroxybenzoic acid or a derivative thereof may be used in combination with one or more of vitamin B.sub.12 (cyano-cobalamin), folic acid (pteroylglutamic acid) or vitamin C (ascorbic acid) for the prevention or treatment of a retroviral infection presenting with 1 or more opportunistic infections. The active ingredient 3-amino-4-hydroxybenzoic acid is suitable for use against retroviral infection, in particular HIV wherein a patient presents without opportunistic infection. In combination with one or more of vitamin B.sub.12, folic acid or vitamin C, preferably all three, 3-amino-4-hydroxybenzoic acid is suitable for the prevention or treatment of a retroviral infection (preferably HIV) which presents with one or more opportunistic infections. Additional adjuvant active ingredients and/or adjuvant drugs may be given to patients presenting with opportunistic infections such as T.B., P.C.P., cryptococcal meningitis, dysentery etc.

Brief Summary Text (44):
The present invention also provides a pharmaceutical composition for oral or injectable administration which comprises 3-amino-4-hydroxybenzoic acid or a derivative thereof in combination with a pharmaceutically acceptable carrier, together with any of vitamin B.sub.12, folic acid, vitamin C or a combination of two or more thereof. Preferably, the 3-amino-4-hydroxybenzoic acid is present in a pharmaceutical composition in an

amount of from 25 to 200 mg, more preferably in an amount of 25, 50, 100 or 200 mg. These doses are appropriate for the most effective concentration for treatment of retroviral disease, particularly HIV.

Brief Summary Text (45):
Preferably the composition includes vitamin B.sub.12, folic acid and vitamin C. The parabens or esters of parahydroxybenzoic acid are known as having bacteriostatic properties. The chemical structure of 3-amino-4-hydroxybenzoic acid is parahydroxybenzoic acid with an additional amino group at C-3. Thus 3-amino-4-hydroxybenzoic acid or a derivative thereof also has bacteriostatic effect. This effect is useful in the treatment of additional opportunistic bacterial infections, preferably in combination with one or more of vitamin B.sub.12, folic acid and vitamin C.

Brief Summary Text (46):
Preferably the pharmaceutical composition comprises 3-amino-4-hydroxybenzoic acid in combination with up to 20 mcg of vitamin B.sub.12, up to 10 mg of folic acid and up to 50 mg of vitamin C. Even more preferably the composition comprises 25, 50, 100 or 200 mcg of 3-amino-4-hydroxybenzoic acid in combination with 10 mcg of vitamin B.sub.12, 5 mg of folic acid and 25 mg of vitamin C.

Detailed Description Text (14):
(1) B.N. was a 30 year old teacher whose wife died in April 1991 of AIDS. He presented with general weakness, weight loss, easy fatigability on exertion, recurrent tonsillitis, mouth ulcers, cervical lymphadenopathy, itchy skin rash and pain in swallowing food. His weight rose from 44-48 kg and haemoglobin rose from 11.69% to 16% after treatment. Lymphocytes rose relatively from 39% to 49%. His signs and symptoms were over by six months of treatment. Follow-up one and half years later showed that he had not lost a single working day because of the sickness.

CLAIMS:

6. A pharmaceutical composition comprising:

(a) 3-amino-4-hydroxybenzoic acid or derivative thereof;

(b) a pharmaceutically acceptable carrier; and

(c) an additive selected from the group consisting of vitamin B.sub.12, folic acid, vitamin C, or a mixture thereof.

9. The pharmaceutical composition according to claim 6, wherein the upper limit of vitamin B.sub.12 is 20 mcg, the upper limit of folic acid is 10 mg and the upper limit of vitamin C is 50 mg.

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L7: Entry 112 of 146 File: USPT Dec 10, 2002

US-PAT-NO: 6491949
DOCUMENT-IDENTIFIER: US 6491949 B2

TITLE: Osmotic device within an osmotic device

DATE-ISSUED: December 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Faour; Joaquina	Buenos Aires			AR
Coppari; Marcelo A.	Buenos Aires			AR

US-CL-CURRENT: 424/473; 424/468

L5: Entry 4 of 6 File: USPT Apr 16, 2002

DOCUMENT-IDENTIFIER: US 6372249 B1
TITLE: Senscent cell-derived inhibitors of DNA synthesis

Detailed Description Text (146):
In a similar manner, antimetbolites such as the folate antagonists (e.g., methotrexate, etc.), purine analogs (e.g., cladribine, fludarabine phosphate, pentostatin, etc.), purine antagonists (e.g., 6-mertcaptopurine, 6-thioguanine, etc.) and pyrimidine antagonists (e.g., 5-fluorouracil, 5-fluorodeoxyuridine, cytarabine, etc.) act on cells in S phase. The efficacy of these agents may be enhanced through the adjunct use of SDI-1 molecules.

Detailed Description Text (170):
The antisense and other SDI inhibitor molecules of the present invention may be used to stimulate the proliferation of spermatocytes, or the maturation of oocytes in humans or animals, and thus, may be used to increase the fertility of a recipient. Conversely, SDI molecules and their analogs can be used to inhibit gametogenesis in males or females, and thus can be used as contraceptive agents to induce infertility in males or females. Such use also provides the benefit of attenuating the replication and proliferation of virally (e.g., HIV, etc.) infected cells, and hence serves to lessen the probability of contracting viral diseases (e.g., AIDS, etc.).

Detailed Description Paragraph Table (6):
TABLE 6 Correlation between SDI-1 mRNA Level and Inhibition of DNA synthesis % SDI-1 Cell Line Inhibition mRNA level P53 Status MADH 041 95 .+-. 4 Not Mutant Detectable SAOS2 47 Not Done Mutant TE85 75 .+-. 7 Not Mutant Detectable T98G 35 .+-. 5 Not Mutant Detectable Hela 60 .+-. 5 Low HPV-18 infected A1698 15 .+-. 3 Normal Wild-type UABC023 57 .+-. 6 Low Unknown Ser 31 .fwdarw. Arg 31 Homozygous GM639 78 Normal SV40-transformed GM847 21 Normal SV40-transformed Ser31 .fwdarw. Arg 31 Heterozygous RN13 No Inhibition Normal Unknown PR282 No Inhibition Normal Unknown